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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,166	08/31/2001	David R. Elmaleh	MGA-003.01	1584

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,166	ELMALEH ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,11 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Any rejection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10, 11 and 25-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended to recite that the targeted oligonucleotide constructs of the claims have essentially no ability to cross the blood-brain barrier. Applicant states that support for this amendment can be found in the examples, wherein an exemplified embodiment comprising an antisense oligonucleotide conjugated to a radioisotope does not exhibit uptake into the brain. The specification does not contemplate constructs comprising a targeting moiety that is an antibody, a lectin, a ligand, a sugar, a steroid, a hormone, a nutrient, a small molecule or a protein that do not cross the blood-brain barrier. Applicant has not provided a representative sample of the claimed genus of compounds that do not cross the blood-brain barrier. The skilled

artisan would not be led to envision the claimed constructs as failing to cross the blood-brain barrier based solely on the failure of the exemplified embodiment to do so, thus applicant has not demonstrated possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5, 8, 10, 11, 25-28, 30-32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuijpers et al (EP 0 490 434).

Claim 1 is directed to a targeted oligonucleotide construct comprising a targeting moiety, an oligonucleotide complementary to a nucleic acid of interest and an imaging agent suitable for use in PET, SPECT or MRI. Claim 4 states the oligonucleotide is an antisense oligonucleotide or oligonucleotide analog modified to enhance its efficacy, pharmacokinetic properties or physical properties. Claim 5 states the imaging agent is a radiolabel chosen from a list of radioisotopes. Claim 8 recites that the construct of claim 1 further comprises a therapeutic agent. Claim 11 limits claim 8 by reciting

limitations identical to those of claim 4. Claims 25-28 limit claim 1 and claims 30-32 and 34 limit claim 11 by reciting specific modifications to the antisense oligonucleotide portion of the construct.

Kuijpers et al. disclose phosphorothioate antisense oligonucleotides conjugated with a radioisotope. Kuijpers et al. disclose ^{123}I and ^{131}I as specific radioisotopes. These labeled oligonucleotides are disclosed as being useful for targeted therapy of tumors. Kuijpers et al. disclose that the labeled oligonucleotides is targeted to a tumor cell by binding to an antibody oligonucleotide conjugate wherein the labeled oligonucleotide then enters the cell as a therapeutic agent (see scheme 1). The instant specification discloses at page 9 that a targeted construct comprises at least two components that are covalently connected. Thus, Kuijpers et al. disclose a construct containing a targeting moiety that is an antibody, an oligonucleotide and an imaging agent suitable for use in PET, SPECT or MRI. The antisense oligonucleotide of Kuijpers et al. is a therapeutic agent that is derivatized with phosphorothioate, which increases nuclease resistance and is specific for mRNA, meeting the limitations of claims 25-28, 30-32 and 34. Although Kuijpers et al. is silent with regard to the ability of the disclosed constructs to cross the blood-brain barrier, Moffett et al. teach that the endothelial cells lining brain capillaries have a low permeability to ions and small organic solutes. Nucleic acids are not only larger than small organic molecules but are also charged. Opalinska et al. further teach that the ability to deliver nucleic acids into any type of cell is limited (see page 511). Based on the teachings of Moffett et al. and

Opalinska et al., the skilled artisan would recognize that the constructs disclosed by Kuijpers et al. would have essentially no ability to cross the blood-brain barrier.

Thus, Kuijpers et al. disclose and anticipate claims 1, 4, 5, 8, 10, 11, 25-28, 30-32 and 34.

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Kayyem et al. (US 6,232,295).

Claim 1 is directed to a targeted oligonucleotide construct comprising a targeting moiety, an oligonucleotide complementary to a nucleic acid of interest and an imaging agent suitable for use in PET, SPECT or MRI. Claims 2, 3 and 5-7 limit claim 1 by reciting particular types of imaging agents.

Kayyem et al. disclose contrast agent and gene delivery vehicles. The delivery vehicles comprise two polymeric compounds of differing charge with a contrast agent and a targeting moiety attached to one of the polymeric compounds. Kayyem et al. disclose that one of the polymeric compounds can be a nucleic acid so that the delivery vehicle delivers both genetic material and a contrast agent to a cell and is useful for gene therapy. Kayyem et al. disclose at column 4, lines 1-16 that the contrast agent is one suitable for MRI or PET and includes paramagnetic metals such as iron and gadolinium or radioisotopes such as ^{68}Ga or ^{99}Tc. At column 4, lines 56-62 Kayyem et al. disclose that the targeting moiety includes antibodies, ligands, hormones and peptides. Thus, Kayyem et al. disclose a construct containing a targeting moiety, an oligonucleotide and an imaging agent suitable for use in PET, SPECT or MRI. Although

Kayyem et al. is silent with regard to the ability of the disclosed constructs to cross the blood-brain barrier, Moffett et al. teach that the endothelial cells lining brain capillaries have a low permeability to ions and small organic solutes. Nucleic acids are not only larger than small organic molecules but are also charged. Opalinska et al. further teach that the ability to deliver nucleic acids into any type of cell is limited (see page 511). Based on the teachings of Moffett et al. and Opalinska et al., the skilled artisan would recognize that the constructs disclosed by Kayyem et al. would have essentially no ability to cross the blood-brain barrier.

Thus, Kayyem et al. disclose and anticipate claims 1-3 and 5-7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 8, 10, 11 and 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuijpers et al. as applied to claims 1, 4, 5, 8, 10, 11, 25-28, 30-32 and 34 above, and further in view of Gewirtz et al. (US 5,098,890, of record) and Low et al. (US 5,994,320, of record).

Claims 1, 4, 5, 8, 10, 11, 25-28, 30-32 and 34 are described in the 102 rejection over Kuijpers et al. Claims 29 and 33 limit claims 4 and 8, respectively, by reciting that

the oligonucleotide portion of the construct is an antisense specific for the C-myb, N-myc, C-myc or PSA genes.

The teachings of Kuijpers et al. are described in the 102 rejection over this reference. Kuijpers et al. do not teach oligonucleotide constructs containing oligonucleotides that are antisense to C-myb, N-myc, C-myc or PSA genes.

Gewirtz et al. and Low et al. each teach antisense directed to C-myb. Gewirtz et al. teach (see abstract) that oligonucleotides targeted to C-myb are useful in treating hematologic neoplasms. Low et al. teach at column 1, line 15 through column 2, line 25 that C-myb is involved in cellular proliferation and differentiation and that antisense to C-myb is known to inhibit proliferation of several cell lines.

It would have been obvious to one of ordinary skill in the art to use the constructs taught by Kuijpers et al. as useful in targeting oligonucleotides to tumors in order to deliver a C-myb oligonucleotide to a tumor. Because Kuijpers et al. teach a construct for targeting tumor cells and because Low et al. and Gewirtz et al. teach that C-myb is useful in treating cancers, one of ordinary skill in the art would have been motivated to target a C-myb antisense sequence to a tumor using the construct of Kuijpers et al. in order to obtain enhanced delivery of the sequence to tumor cells. One of ordinary skill in the art would have had a reasonable expectation of success in making the construct of Kuijpers et al. with an antisense targeted to C-myb because Kuijpers et al. actually make their construct using techniques well-known in the art and Low et al. and Gewirtz et al. actually make antisense to C-myb using similar synthetic techniques.

Thus, the invention of claims 1, 4, 5, 8, 10, 11 and 25-34 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
February 15, 2006

J.D. SCHULTZ, Ph.D.
PATENT EXAMINER